Point of Care Clinical Risk Score to Improve the Negative Diagnostic Utility of an Agatston Score of Zero: Averting the Need for Coronary Computed Tomography Angiography

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Abstract: BACKGROUND Coronary artery calcification is a marker of underlying atherosclerotic vascular disease. The absence of coronary artery calcification is associated with a low prevalence of obstructive coronary artery disease (CAD), but it cannot be ruled out completely. We sought to develop a clinical tool that can be added to Agatston score of zero to rule out obstructive CAD with high accuracy. METHODS We developed a clinical score retrospectively from a cohort of 4903 consecutive patients with an Agatston score of zero. Patients with prior diagnosis of CAD, coronary percutaneous coronary intervention, or surgical revascularization were excluded. Obstructive CAD was defined as any epicardial vessel diameter narrowing of 50%. The score was validated using an external cohort of 4290 patients with an Agatston score of zero from a multinational registry. RESULTS The score consisted of 7 variables: age, sex, typical chest pain, dyslipidemia, hypertension, family history, and diabetes mellitus. The model was robust with an area under the curve of 0.70 (95% CI, 0.65-0.76) in the derivation cohort and 0.69 (95% CI, 0.65-0.72) in the validation cohort. Patients were divided into 3 risk groups based on the score: low (6), intermediate (7-13), and high (14). Patients who score 6 have a negative likelihood ratio of 0.42 for obstructive CAD, whereas those who score 14 have a positive likelihood ratio of >5.5 for obstructive CAD. The outcome was ruled out in >98% of patients with a score 6 in the validation cohort. CONCLUSIONS We developed a score that may be used to identify the likelihood of obstructive CAD in patients with an Agatston score of zero, which may be used to direct the need for additional testing. However, the results of this retrospective analysis are hypothesis generating and before clinical implementation should be validated in a trial with a prospectively collected data.

DOI: https://doi.org/10.1161/CIRCIMAGING.118.008737

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DOI: https://doi.org/10.1161/CIRCIMAGING.118.008737

Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Point of Care Clinical Risk Score to Improve the Negative Diagnostic Utility of an Agatston Score of Zero

Averting the Need for Coronary Computed Tomography Angiography

See Editorial by Ramchand, Jaber, and Hachamovitch

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BACKGROUND: Coronary artery calcification is a marker of underlying atherosclerotic vascular disease. The absence of coronary artery calcification is associated with a low prevalence of obstructive coronary artery disease (CAD), but it cannot be ruled out completely. We sought to develop a clinical tool that can be added to Agatston score of zero to rule out obstructive CAD with high accuracy.

METHODS: We developed a clinical score retrospectively from a cohort of 4903 consecutive patients with an Agatston score of zero. Patients with prior diagnosis of CAD, coronary percutaneous coronary intervention, or surgical revascularization were excluded. Obstructive CAD was defined as any epicardial vessel diameter narrowing of ≥50%. The score was validated using an external cohort of 4290 patients with an Agatston score of zero from a multinational registry.

RESULTS: The score consisted of 7 variables: age, sex, typical chest pain, dyslipidemia, hypertension, family history, and diabetes mellitus. The model was robust with an area under the curve of 0.70 (95% CI, 0.65–0.76) in the derivation cohort and 0.69 (95% CI, 0.65–0.72) in the validation cohort. Patients were divided into 3 risk groups based on the score: low (≤6), intermediate (7–13), and high (≥14). Patients who score ≤6 have a negative likelihood ratio of 0.42 for obstructive CAD, whereas those who score ≥14 have a positive likelihood ratio of >5.5 for obstructive CAD. The outcome was ruled out in >98% of patients with a score ≤6 in the validation cohort.

CONCLUSIONS: We developed a score that may be used to identify the likelihood of obstructive CAD in patients with an Agatston score of zero, which may be used to direct the need for additional testing. However, the results of this retrospective analysis are hypothesis generating and before clinical implementation should be validated in a trial with a prospectively collected data.

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Key Words: chest pain ■ coronary artery disease ■ diabetes mellitus ■ humans ■ registries

https://www.ahajournals.org/journal/circimaging

CLINICAL PERSPECTIVE

Traditionally, coronary artery calcification scoring has been used in the asymptomatic population to refine risk of future adverse cardiovascular events. Most recently, the American Heart Association issued guidelines for therapy based on coronary artery calcification. The utility of coronary artery calcification in the symptomatic population and how it may be used to guide downstream testing is lacking. The results of our study suggest that the combination of a clinical model and coronary artery calcification score of zero may effectively eliminate the need of additional testing. A prospective trial is needed to verify these results.

Coronary artery calcification (CAC) is a marker of underlying coronary artery atherosclerosis and an independent predictor of future cardiovascular events.[1–4] The absence of CAC is prognostically important and identifies a population at low risk of future cardiovascular events.[1,2,5–9] Despite the low rates of future cardiovascular events, the absence of CAC does not have sufficient negative predictive value for widespread use as a single test for clinical risk stratification among symptomatic patients for whom there is a suspicion of obstructive coronary artery disease (CAD).[10]

Previous studies have demonstrated that, despite the absence of CAC, 1.4% to 7% of symptomatic individuals have obstructive CAD.[11–13] Thus, clinicians are often unwilling to use the absence of CAC to halt additional testing in symptomatic patients with suspected CAD.

Image acquisition for CAC is routinely performed before coronary computed tomographic angiography (CCTA) and quantified using the Agatston method.[14] We sought to derive and validate a clinical tool that can be used in symptomatic patients without CAC (Agatston score, 0) to help to rule out obstructive CAD and potentially limit unnecessary downstream testing.

METHODS

Study Design and Eligibility

Using a cardiac computed tomography (CT) registry,[15] we identified a derivation cohort comprised of patients with an Agatston score of zero who also underwent coronary CT angiography (CCTA). A nonoverlapping subgroup from Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter registry with Agatston score of zero was used for validation.[16] We included only Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter registry centers with complete CCTA data and data on chest pain typicality and cardiac risk factors. Patients with a history of CAD, myocardial infarction, or revascularization were excluded. Additionally, we excluded patients being worked up for acute presentation with chest pain or to rule out acute coronary syndrome.

The study was approved by our institutional review board, and written, informed consents were obtained by all enrolled patients. Data supporting the findings of this study may be available from the corresponding author on reasonable request.

Clinical Definitions

Clinical assessment done at the time of CCTA included medical history, physical findings, and available laboratory studies.[15,16] Chest pain typicality was defined according to the classification proposed by Diamond and Forrester.[17] The presence of cardiac risk factors was obtained through patient self-reporting and medical records. Hypertension was defined as known history of diagnosis of hypertension (systolic blood pressure ≥140 mm Hg) or being treated for hypertension. Diabetes mellitus was defined as history of type I or type II diabetes mellitus or the use of hypoglycemic agents. Dyslipidemia was defined as a self-reported history of a known diagnosis of dyslipidemia or treatment with lipid-lowering agents. Family history of CAD was defined as diagnosis of CAD in a first-degree relative (age of <55 years for men and <65 years for women).

The pretest probability of obstructive CAD (≥50% luminal stenosis) was calculated for all patients according to age, sex, and typicality of chest pain using updated Diamond-Forrester risk model.[18]

Coronary Calcification and Computed Tomographic Angiography

CAC and CCTA images were acquired using single or dual source ≥64 slice CT scanners.[15,16] Scans were interpreted by physician experts at each site.[19,20] Coronary calcification was quantified using the Agatston method.[14] Coronary artery segmental luminal diameter was graded on a 4-point score (normal, mild [<50% stenosis], moderate [50%–69% stenosis], or severe [≥70% stenosis]), and patients with a stenosis of ≥50% were categorized as having obstructive CAD. Because most of our data were collected before the publication of the CAD Reporting and Data System, minimal (1%–24%) and mild (25%–49%) stenoses were grouped together as a mild stenosis (0%–49%).[10]

Statistical Analysis

To compare the clinical characteristics of patients, we used Fisher exact test for categorical variables and *t* test for continuous variables. Categorical variables are presented as proportions with percentages, and continuous variables are presented as means with SDs. Statistical significance threshold was set at $P<0.05$. Multiple imputations were performed for the missing values. Centers with large proportions of missing data on chest pain typicality or any of the risk factors for CAD were excluded from the validation cohort. All statistical procedures were performed using SAS 9.4 statistical software (SAS Institute, Cary, NC).

Model Derivation

To avoid data-driven model development, we specified our clinical variables apriori.[21] A group of practicing cardiologists was

surveyed for 5 to 10 clinical predictors from a list of candidate clinical variables with potential association with CAD. This list included demographic data, known diagnoses and risk factors, symptoms, medications, physical assessment, and electrocardiographic findings. Clinical variables with the highest number of votes (age, sex, typical chest pain, hyperlipidemia, hypertension, diabetes mellitus, current smoking, and family history) were included in a multivariable logistic regression model. Interaction between sex and other variables in the multivariable model was examined. Receiver operating characteristic curve for the multivariable model was generated. The discriminative ability of the model was assessed using area under the curve and the corresponding C statistics. Model goodness of fit was assessed using Hosmer-Lemeshow statistics.

Development of the Scoring System

A point scoring system was derived from the proposed multivariable model based on the regression coefficients. We assigned points for each variable according to its regression coefficient, with 1 point for the smallest regression coefficient, which served as the least common denominator for assigning point values for the score items. We used methods described by Sullivan et al[22] and Le Gal et al.[23] We computed the score for each patient and evaluated the classification ability of the developed score using the sensitivity, specificity, positive and negative predictive values, and the likelihood ratios with CIs of each level of the score. We then defined the risk thresholds for low- and high-risk groups based on the negative and positive likelihood ratios, respectively, in a post hoc procedure. The calibration of the score was assessed by plotting the predicted risk of obstructive CAD against the observed one. The goodness of fit of the developed score was assessed using Hosmer-Lemeshow statistics where $P>0.05$ indicates adequate fit of the score. We constructed a nomogram of the developed risk score and a graphic plot of the risk score thresholds versus the likelihood ratio for clinical use (Figures I and II in the Data Supplement).

Score Validation

We applied the score externally and assessed the applicability of the scoring system in the validation cohort. We calculated the proportion of patients classified by the developed score and the observed risk of obstructive CAD for each risk group in the derivation and validation cohorts. We calculated the risk of all-cause mortality for each risk group in the validation cohort based on data of a median follow-up of 2 years.

RESULTS

A total of 44 125 consecutive patients (17 000 from the derivation cohort registry and 27 125 patients from the CONFIRM registry (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) representing the validation cohort) were screened. After excluding patients with a history of CAD, coronary revascularization, cardiac transplantation, and congenital heart disease, we identified 4903 eligible patients with an Agatston score of zero in the derivation cohort, with 2.3% (n=112) having obstructive CAD (diameter stenosis, ≥50%). A nonoverlapping 8021 patients from Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter registry were found with an Agatston score of zero. Centers with a large proportion of missing data were excluded. The final validation cohort comprised of 4290 patients, with 4.8% (n=207) having obstructive CAD (Table 1). The proportion of imputed data was <5% of the total observations in both derivation and validation cohorts.

Derivation Cohort

The prespecification survey resulted in selection of age, sex, typical chest pain, family history, dyslipidemia, hypertension, and diabetes mellitus to be included in the multivariable logistic regression model (Table 2). Current smoking was excluded from the multivariable model because of the resulting paradoxical association between smoking and the outcome of obstructive CAD, which is clinically nonplausible. There was insignificant interaction between sex and other variables. The proposed model had an area under the receiver operating characteristic curve of 0.70 (95% CI, 0.65–0.76) in the derivation cohort (Figure 1A).

Score Development

Each variable was assigned a value derived from the corresponding regression coefficient in the multivariable model (Table 3). Based on the generated score (range, 0–20), the predicted probability for prevalence of obstructive CAD ranged from 0.45% (95% CI, 0.26–0.77) to 18% (95% CI, 10.78–28.30). The diagnostic ability for each score threshold in the model was calculated (Table 4), and thresholds were grouped into 3 categories (low [≤6], intermediate [7–13], and high [≥14]) based on the positive and negative likelihood ratios (Table 5). Patients with a score of ≤6 have a high negative predictive value (99%) and a low negative likelihood ratio (0.42; Table 5). Conversely, patients for whom the score was ≥14 have a specificity of 98% and a positive likelihood ratio of >5 for obstructive CAD (Table 5).

Score Validation

Using an external validation cohort, the score demonstrated an acceptable discriminative performance with an area under the receiver operating characteristic curve of 0.69 (95% CI, 0.65–0.72; Figure 1B). The proportion of patients in each risk category in the validation cohort is similar to that in the derivation cohort but slightly higher prevalence of obstructive CAD consistent with the overall higher prevalence of obstructive CAD in the validation cohort (Table 5). The score had a good calibration between predicted and observed risks of obstructive CAD in the derivation and validation cohorts particularly at low- and intermediate-risk categories (Figure 2). The risk of death of any cause in

Table 1. Clinical Characteristics of Derivation and Validation Cohorts

	Derivation Cohort			Validation Cohort		
	No Obstructive CAD (n=4791)	Obstructive CAD (n=112)	*P* Value	No Obstructive CAD (n=4083)	Obstructive CAD (n=207)	*P* Value*
Age, y	53±10.3	53±10	0.588	52±12	60±12	0.0001
Men	1993 (42)	65 (58)	0.0006	1967 (48)	111 (54)	0.100
Pretest probability of CAD	0.21±0.36	0.32±0.32	0.003	0.30±0.26	0.36±0.29	0.006
Body mass index, kg/m^2	29±6	30±5	0.412	28±5	29±6	0.007
Chest pain			0.0002			0.164
Typical	370 (8)	22 (20)		407 (10)	23 (11)	
Atypical/noncardiac	2628 (55)	51 (46)		2151 (53)	87 (54)	
Shortness of breath	2935 (61)	61 (54)	0.250	792 (19)	47 (23)	0.023
Asymptomatic	871 (18)	16 (14)	0.113	1111 (27)	57 (25)	0.124
Family history	2194 (46)	56 (50)	0.389	1481 (36)	100 (49)	0.001
Hypertension	1838 (38)	54 (48)	0.040	1544 (38)	104 (51)	0.0003
Hyperlipidemia	1970 (41)	67 (60)	0.0001	1644 (40)	129 (63)	0.0001
Current smoking	650 (14)	15 (13)	0.820	663 (16)	32 (16)	0.922
Diabetes mellitus	432 (9)	15 (13)	0.132	299 (7)	43 (21)	0.0001
Aspirin	2010 (42)	63 (56)	0.004	700 (17)	30 (15)	0.002
β-Blockers	1601 (33)	47 (42)	0.068	663 (16)	19 (9)	0.560
Lipid-lowering agents	1408 (29)	49 (44)	0.002	587 (14)	25 (2)	0.043
Resting ECG						
Ischemic changes†	1334 (28)	23 (21)	0.108	NA	NA	

CAD indicates coronary artery disease.
**P* value was calculated based on effective sample size.
†Ischemic changes: anterior or inferior q wave and nondynamic ST-segment deviation.

the low- and intermediate-risk groups in the validation cohort was 0.51% and 0.58%, respectively, compared with 2% in the high-risk group (*P*=0.02).

When we included symptomatic patients only, there was no significant difference in the discriminative performance of the score with an area under the receiver operating characteristic curve of 0.67 in both the derivation (95% CI, 0.62–0.73) and validation (95% CI, 0.62–0.71) cohorts.

DISCUSSION

The results of our analysis demonstrate that not all patients with a zero calcium score are equal. Our model demonstrates that an Agatston score of zero can be used to exclude obstructive CAD but also identify a group where CAC alone cannot be used to exclude CAD.

This project is novel because it addresses an unmet need of how a zero calcium score can be incorporated into a clinical strategy among patients with suspected CAD so that additional testing might be averted. The developed tool includes clinical variables that are readily available for most of the patients on clinical assessment and calcium score quantification performance. The relationship between current smoking and the outcome of obstructive CAD in our multivariable model was not clinically plausible, and thus current smoking was excluded

Table 2. Multivariable Clinical Model for Obstructive Coronary Artery Disease

	β	SE	Odds Ratio	Lower CI	Upper CI	*P* Value
Intercept	–5.3101	0.6457	…	…	…	
Age, y	0.00935	0.0104	1.009	0.989	1.030	0.3665
Men	0.8024	0.2105	2.231	1.477	3.370	0.0001
Typical chest pain	1.0549	0.2779	2.872	1.666	4.950	0.0001
Hyperlipidemia	0.6276	0.2077	1.873	1.247	2.814	0.0025
Hypertension	0.2091	0.2011	1.233	0.831	1.828	0.2984
Family history	0.2331	0.1971	1.262	0.858	1.858	0.2370
Diabetes mellitus	0.1597	0.2954	1.173	0.657	2.093	0.5889

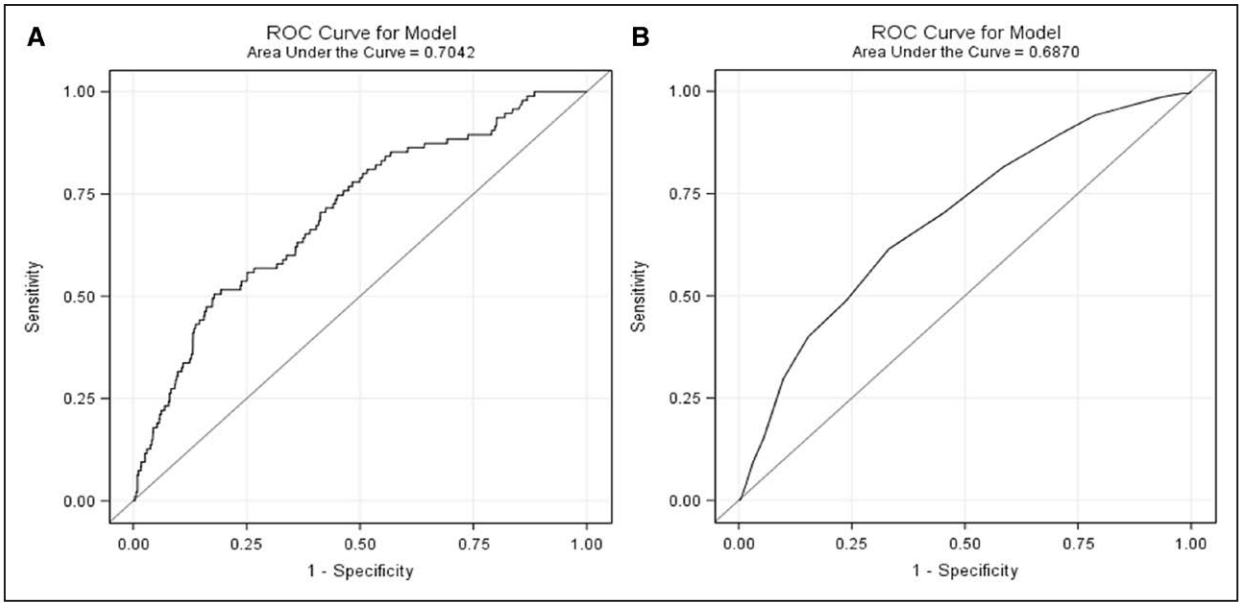

Figure 1. Receiver operating characteristic (ROC) curve of the model to predict obstructive coronary artery disease in derivation and validation cohorts. Our model has an area under the ROC curve of 0.70 (CI, 0.65–0.76) in the derivation cohort (**A**) and 0.69 (95% CI, 0.65–0.72) in the validation cohort (**B**), which demonstrates a robust discriminative ability.

from our tool. This paradoxical relationship could be due to issues surrounding data collection and classification of smoking status. Younger patients who smoke but with an overall lower risk profile are more likely to be referred for CCTA although there was no interaction between current smoking and other variables in our model. Model specification was done a priori through surveying a group of practicing cardiologists to avoid data-driven selection of predictors and model overfitting.[24] We used the likelihood ratios for risk classification given the low prevalence of the outcome in the derivation cohort (2%) and the limitations of the sensitivity and specificity in such case. When validated externally in a multicenter cohort, it showed an acceptable discriminative and classification performance. This indicates both validity and transportability of the developed score. Our score appeared to be more useful in identifying the group with low probability of having obstructive CAD and thereby can be used as a tool to guide the downstream testing in this group. Prognostically, patients in the low- and intermediate-risk groups had a lower risk of all-cause mortality compared with those in the higher risk group when followed up for a median follow-up time of 2 years in the validation cohort.

Table 3. Obstructive CAD Score in Patients With Agatston Score of Zero

Variable	Scoring Point
Age, y	
<30	0
30–39	1
40–49	2
50–59	3
60–69	4
≥70	5
Men	4
Typical chest pain	5
Dyslipidemia	3
Hypertension	1
Family history of CAD	1
Diabetes mellitus	1

Clinical probability: low risk, ≤6 points; intermediate risk, 7 to 13 points; high risk, ≥14 points. CAD indicates coronary artery disease.

Coronary Artery Calcification

CAC has important diagnostic and prognostic implications. CAC is a marker of atherosclerotic disease and is associated with future cardiovascular events and all-cause mortality.[1–5,25,26] When added to conventional risk factors, calcium score improves the performance of prediction models for cardiovascular events and improves the reclassification of individuals' risks. Adding the Agatston score to the Framingham risk score led to significant reclassification of individuals to higher or lower risk categories.[27–30]

Clinical Utility of an Agatston Score of Zero

The Agatston score of zero has been investigated in several studies of asymptomatic and symptomatic participants.[1,2,4–6] Raggi et al[5] reported low annual coronary event rates of 0.11% for Agatston score of zero compared with 4.8% for score of ≥400 in asymptomatic patients. Among 3409 patients with Agatston score of zero in the MESA (Multi-Ethnic Study of Atherosclerosis), only 0.4% devel-

Table 4. Operating Characteristics for Thresholds of Obstructive Coronary Artery Disease Score

Score	Sensitivity	Specificity	PPV	NPV	PLR	NLR
0	1.00 (0.999 to 1.000)	0.0	0.023 (0.019 to 0.027)	…	1.00	…
1	1.00 (0.979 to 1.000)	0.002 (0.001 to 0.004)	0.023 (0.019 to 0.027)	1.000 (0.720 to 1.000)	1.00	…
2	0.99 (0.958 to 1.000)	0.010 (0.008 to 0.014)	0.023 (0.019 to 0.028)	0.980 (0.894 to 1.000)	1.001 (0.982 to 1.020)	0.877 (–0.953 to 2.699)
3	0.98 (0.948 to 1.000)	0.049 (0.044 to 0.056)	0.024 (0.019 to 0.028)	0.992 (0.970 to 1.000)	1.033 (1.005 to 1.062)	0.358 (–0.165 to 0.887)
4	0.96 (0.911 to 0.990)	0.133 (0.124 to 0.143)	0.025 (0.020 to 0.030)	0.994 (0.984 to 0.998)	1.112 (1.068 to 1.157)	0.268 (–0.006 to 0.542)
5	0.884 (0.810 to 0.937)	0.237(0.225 to 0.249)	0.026 (0.022 to 0.032)	0.989 (0.981 to 0.994)	1.158 (1.073 to 1.242)	0.490 (0.223 to 0.758)
6	0.866 (0.789 to 0.923)	0.318 (0.305 to 0.331)	0.029 (0.023 to 0.035)	0.990 (0.984 to 0.995)	1.269 (1.168 to 1.371)	0.421 (0.210 to 0.633)
7	0.786 (0.698 to 0.858)	0.431 (0.417 to 0.445)	0.031 (0.025 to 0.038)	0.990 (0.983 to 0.993)	1.381 (1.235 to 1.528)	0.497 (0.309 to 0.865)
8	0.679 (0.584 to 0.764)	0.577 (0.563 to 0.591)	0.036 (0.029 to 0.045)	0.990 (0.982 to 0.992)	1.605 (1.380 to 1.829)	0.557 (0.397 to 0.716)
9	0.563 (0.466 to 0.656)	0.703 (0.690 to 0.716)	0.042 (0.033 to 0.054)	0.987 (0.981 to 0.989)	1.895 (1.555 to 2.235)	0.622 (0.483 to 0.761)
10	0.473 (0.378 to 0.570	0.794 (0.782 to 0.805)	0.051 (0.038 to 0.066)	0.985 (0.980 to 0.988)	2.292 (1.798 to 2.786)	0.664 (0.540 to 0.788)
11	0.393 (0.302 to 0.490)	0.865 (0.855 to 0.874)	0.064 (0.047 to 0.084)	0.984 (0.980 to 0.987)	2.905 (2.162 to 3.648)	0.702 (0.591 to 0.813)
12	0.214 (0.142 to 0.302)	0.918 (0.910 to 0.925)	0.057 (0.037 to 0.084)	0.980 (0.976 to 0.984)	2.606 (1.591 to 3.620)	0.856 (0.768 to 0.944)
13	0.143 (0.084 to 0.222)	0.958 (0.952 to 0.964)	0.074 (0.043 to 0.117)	0.980 (0.975 to 0.983)	3.405 (1.694 to 5.115)	0.894 (0.822 to 0.967)
14	0.116 (0.63 to 0.190)	0.979 (0.974 to 0.983)	0.114 (0.062 to 0.187)	0.979 (0.975 to 0.983)	5.505 (2.312 to 8.697)	0.903 (0.839 to 0.967)
15	0.063 (0.026 to 0.124)	0.987 (0.983 to 0.990)	0.100 (0.041 to 0.195)	0.978 (0.973 to 0.982)	4.753 (0.930 to 8.576)	0.950 (0.902 to 0.998)
16	0.027 (0.006 to 0.076)	0.991 (0.988 to 0.993)	0.064 (0.013 to 0.175)	0.978 (0.973 to 0.982)	2.917 (0.656 to 6.489)	0.982 (0.950 to 1.014)
17	0.018 (0.002 to 0.063)	0.996 (0.993 to 0.997)	0.087 (0.012 to 0.280)	0.978 (0.972 to 0.981)	4.074 (–2.143 to 10.291)	0.986 (0.960 to 1.013)
18	0.009 (0.002 to 0.049)	1.000 (0.998 to 1.000)	0.333 (0.008 to 0.906)	0.977 (0.973 to 0.981)	21.38 (–32.921 to 75.698)	0.992 (0.973 to 1.010)
19	0.0	1.000 (0.998 to 1.000)	…	0.977 (0.973 to 0.981)	0.00	1.009 (0.810 to 1.208)

NLR indicates negative likelihood ratio; NPV, negative predictive value; PLR, positive likelihood ratio; and PPV, positive predictive value.

oped any coronary event during the follow-up period of 3 years versus an event rate of 8% for those with Agatston score ≥300.[4] Despite the prognostic utility of zero calcium score as proven by the low cardiovascular event rates, the presence of obstructive CAD among these patients cannot be absolutely ruled out. Several earlier studies reported a prevalence of obstructive CAD in patients with zero calcium score that varied widely from 7% to 38%.[11,31–34] This is likely explained by the high-risk presentations of populations studied and technology used. Villines et al[12] reported a prevalence of 3.5% of obstructive CAD among patients with an Agatston score of zero. More recently, Mittal et al[13] reported a lower prevalence rate of obstructive CAD in patients with zero calcium score of 1.4% in a cohort of mostly asymptomatic patients and patients with atypical presentation.

The diagnostic uncertainty of an Agatston score of zero has limited its clinical use to rule out obstructive CAD. Our proposed clinical risk score when combined with calcium score can improve the diagnostic utility of an Agatston score of zero by allowing it to rule out obstructive CAD with a negative predictive value of 99%. Based on the performance of this risk score, we propose a new management algorithm for workup of suspected CAD when CCTA is considered (Figure 3). For patients presenting for CCTA to rule out obstructive CAD, those with a low risk score (≤6), an Agatston score be performed. In those with an Agatston score of zero, the presence of obstructive CAD can be ruled out with high certainty. Theoretically, this approach will result in lower radiation exposure, eliminate the need for contrast media, and reduce healthcare costs.

Conversely, this model could also be used to identify patients who may require further testing. Those symptomatic patients with an Agatston score of zero

Table 5. Proportions of Patients Classified by Obstructive CAD Risk Score Among Patients With Agatston Score of Zero and Predictive Accuracy of the Score

	Derivation Cohort		Validation Cohort	
Clinical Score	Total Patients, n (%)	Confirmed Obstructive CAD, n (%)	Total Patients, n (%)	Confirmed Obstructive CAD, n (%)
Low risk, ≤6	2090 (42.63)	24 (1.15)	1736 (40.50)	34 (1.96)
Intermediate risk, 7–13	2699 (55.05)	75 (2.78)	2407 (56.11)	152 (6.31)
High risk, ≥14	114 (2.32)	13 (11.40)	147 (3.40)	19 (12.93)

CAD indicates coronary artery disease.

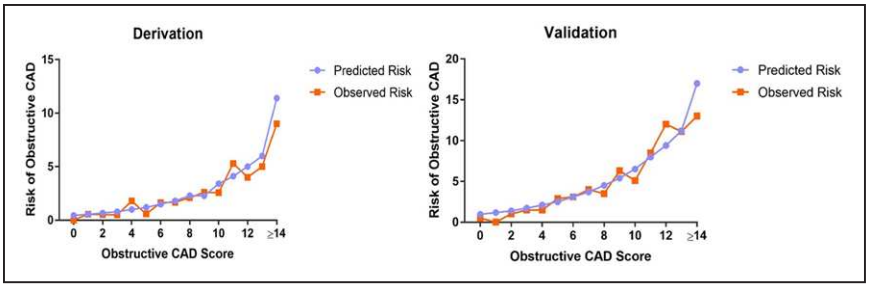

Figure 2. Plot of obstructive coronary artery disease (CAD) score in derivation and validation cohorts.
The developed risk score showed a good calibration between observed and predicted risks at low- and intermediate-risk score categories in the derivation and validation cohorts.

and a score >6 should proceed with CCTA or other testing since obstructive CAD cannot be excluded. As an example, a 50-year-old symptomatic man and a 50-year-old woman with 2 risk factors would both have an intermediate-risk score, despite having an Agatston score of zero.

Limitations

The definition of obstructive CAD was based on the findings from CCTA; therefore, false-positive and false-negative cases are possible. Because most of CCTA studies were performed before the publication of the CAD Reporting and Data System, some of the included patients with typical symptoms may have had long lesions or large volume plaque with luminal stenosis <50%, which could result in ischemia. For the development of our model, we used data collected retrospectively from a tertiary-care center where functional testing for CAD and invasive coronary angiogram are easily accessible; this may introduce referral bias as the cohort has an overall lower risk of obstructive CAD. Our validation dataset was a subgroup with low rates of missing values from a larger international registry. Exclusion of other centers could have affected the representation of the validation cohort. The results of this retrospective analysis are hypothesis generating and before clinical implementation, should be validated in a trial with a prospectively collected data.

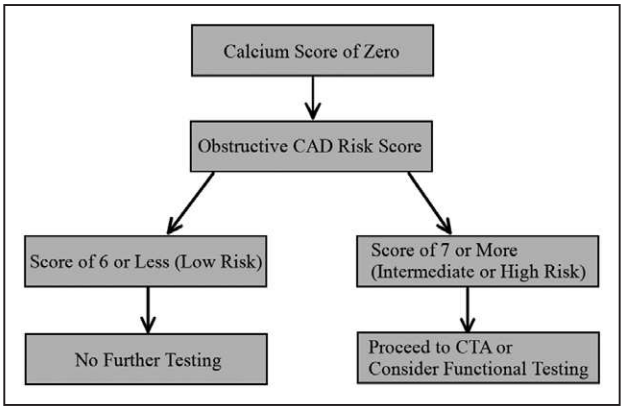

Figure 3. Proposed algorithm for work up of obstructive coronary artery disease (CAD) based on the obstructive CAD risk score.
The proposed algorithm provides an illustration of the use of the obstructive CAD risk score as a clinical decision tool. In patients with zero calcium score, patients with a score of ≤6 points, further testing may not be needed as obstructive CAD can be ruled out with high accuracy. CTA indicates computed tomographic angiography.

Conclusions

We developed a score that may be used to identify the likelihood of obstructive CAD in patients with an Agatston score of zero, which may be used to direct the need for additional testing. However, the results of this retrospective analysis are hypothesis generating and before clinical implementation, should be validated in a trial with a prospectively collected data.

ARTICLE INFORMATION

Received November 28, 2018; accepted July 2, 2019.

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCIMAGING.118.008737.

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Disclosures

Dr Budoff receives grant support from General Electric. Dr Leipsic serves as a consultant and has stock options with Circle Cardiovascular Imaging and Heartflow. Dr Min receives research support from National Institutes of Health, General Electric Healthcare, and Dalio Foundation; serves on the advisory board for General Electric Healthcare and Arineta; and has ownership interest with Cleerly. Dr Chow receives research support from CV Diagnostix and Ausculsciences; educational support from TeraRecon, Inc; and has equity interest in General Electric. The other authors report no conflicts.

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